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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/877,695	06/08/2001	John R. Desjarlais	16380-002001	8902
26161	7590	03/24/2005	EXAMINER	
FISH & RICHARDSON PC 225 FRANKLIN ST BOSTON, MA 02110			MORAN, MARJORIE A	
			ART UNIT	PAPER NUMBER
			1631	

DATE MAILED: 03/24/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/877,695

Applicant(s)

DESJARLAIS, JOHN R.

Examiner

Marjorie A. Moran

Art Unit

1631

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 26 November 2004.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-8, 12-68 is/are pending in the application.
- 4a) Of the above claim(s) 15, 17, 23, 30-37, 57-59, 62, 63 and 66 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-8, 12-14, 16, 18-22, 24-29, 38-56, 60, 61, 64, 65, 67 and 68 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

Election/Restriction

Claims 15, 17, 23, 30-37, 57-59, 62-63 and 66 are again withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected Invention or species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 3/29/04. It is noted that claim 34 is listed as "original" instead of "withdrawn" in the reply filed 11/26/04. As an incorrect claim listing may cause a reply to be considered nonresponsive, applicant is encouraged to carefully review the listed status for all claims in future responses.

A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

An action on the merits of elected claims 1-8, 12-14, 16, 18-22, 24-29, 38-56, 60-61 and 64-65, as they read on the elected species of Monte Carlo and mean field theory design algorithms, follows. Rejections made under 35 USC 112 not reiterated below are hereby withdrawn. Applicant's arguments filed 11/26/04 have been fully considered but they are not persuasive. Arguments as they pertain to specific rejections are addressed below.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 39-40 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. A method of generating a probability matrix wherein a library of proteins are identified, as recited in amended claims 39 and 40, is new matter.

Original claims 39-40 limited a library to be "designed by" various procedures. It was unclear what structural limitation of the library elements was intended by the "design" limitations or if further method steps were intended, as previously set forth. Original claims 57 and 58 (currently withdrawn) recite identifying side chains suitable for a protein structure, but do not recite identification of an entire library of proteins from a probability matrix. The originally filed specification discloses and exemplifies designing and generating proteins and combinatorial libraries; e.g. on pages 26-33, but does not disclose identification of a library of proteins anywhere. Applicant has not set forth support for the newly added limitations of claims 39-40 in the response filed 11/26/04, and none is apparent, as set forth above, therefore the claims are rejected for reciting new matter.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-6, 14, 16, 18-22, 24-29, 38-40, 44-56, 65 and 67-68 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Amended claim 1 recites a step of sampling or evaluating "fitness" of one or more amino acids. Claim 19 recites a step of "evaluating fitness" of amino acids. Claim 56 also recites "evaluating fitness" of rotamers. New claim 67 recites "evaluating fitness" of amino acids by "evaluating fitness" of rotamers. It is unclear what "fitness" is being evaluated in these claims. The term "fitness" is not defined by the specification, and it is unclear whether "fitness" is intended to be a qualitative or quantitative evaluation. For example, is "fitness" associated with energy constraints, torsional constraints, some other physical parameter, fitting or docking to a binding site on another protein or receptor, or some combination of parameters? As it is unclear what "fitness" is to be evaluated, the claims are indefinite.

Claim 48 limits the method of claim 3 to further comprise screening or selecting one or more proteins from the generated combinatorial library. However, claim 48 does not recite any parameters for screening or selecting, such that one skilled in the art would be apprised of the metes and bounds intended by applicant for the protein to be thus chosen. As it is unclear what the protein is intended to be selected or screened for (or against), the claim is indefinite. In response to the argument that methods of screening are well known in the art, it is noted that the rejection is not one of lack of enablement (i.e. that one skilled in the art would not know HOW to screen), but one of

indefiniteness. It is admitted that breadth is not indefiniteness; however, the claims must clearly set forth the metes and bounds intended by applicant for the claimed invention. In the instant case, one skilled in the art would not know what limitations applicants intend for the selected proteins. As previously set forth and reiterated above, one skilled in the art would not know what properties, parameters, etc. applicants intend the proteins to be screened for (or against), therefore the examiner maintains that the claim is indefinite.

The terms "enhanced" and "improved" in claim 50 are relative terms which renders the claim indefinite. The terms "enhanced" and "improved" are not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. In addition, it is still not clear what is intended by an "enhanced" activity (e.g. a higher binding affinity may be considered "enhanced" for a compound which acts as a receptor agonist whereas a lower binding affinity would be considered "enhanced" for an antagonist). For these reasons and those previously set forth, the examiner maintains that the claim is indefinite.

New claim 68 recites the phrase "the single protein sequence" in line 2. There is no antecedent basis for this phrase in the claims, therefore claim 68 is indefinite. Parent claim 3 recites producing a combinatorial library of proteins, not a single protein. It is noted that claim 2 does recite generating a single protein sequence.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 4-8, 12-14, 18-21, 27-29, 41-47, 49, 51-56, 64-65 and 67 are rejected under 35 U.S.C. 102(b) as being anticipated by KOEHL et al. (J. Molec. Biol. (1994) vol. 239, pp. 249-275).

KOEHL teaches a computerized method of generating a global conformational (probability) matrix representing a protein structure (p. 250) wherein an averaged rotamer (backbone) library or ensemble is provided (p. 251), a self consistent mean field theory/algorithm (SCFM) is used to generate possible side chain sequences and to evaluate fitness (potential energy) of all possible rotamers to generate the matrix (pp. 251-252 and 256-257), thus anticipating claims 1, 5, 19, 44, 65 and 67. KOEHL teaches that the protein and/or backbones may be derived from or based on comparison to a natural protein (pp. 254-255), thus anticipating claims 6-7, 14, 20-21, and 27-28. KOEHL further teaches that her matrix calculations comprise information from partition functions (p. 254) and comprise information for all amino acids (p. 259, esp. Table 3), thereby anticipating claims 45 and 47. KOEHL teaches that his method steps may be iterated in multiple cycles, using multiple matrices, until convergence is reached (e.g.; p. 254), and teaches addition and subtraction of free energy to meet

accuracy constraints (pp. 254-258), thus anticipating claims 4, 8, 12-13, 18, 29, 41-43, 46, 49, and 51-56.

In response to the argument set forth in the response of 11/26/04 that KOEHL does not teach generation of a probability matrix for amino acids that represent a “viable sequence space”, it is noted that KEOHL clearly teaches use of a conformational matrix to predict the probability side chain conformations in a method to generate “viable” protein sequences (see her abstract, p. 251 “The conformational matrix”, and pp. 256-257 “Side-chain prediction for a variety of proteins”). Applicant argues that KOEHL starts with conformation of a protein backbone and an amino acid sequence, which presumably differ from the claimed backbone ensemble and generation of protein sequences. As KOEHL teaches that her “backbone” may be an averaged library or ensemble, and specifically teaches generation of a set of protein sequences using SCFM (p. 251), the examiner maintains that KOEHL anticipates these steps. Applicant points to KOEHL’s example and argues that KOEHL does not determine which “other amino acids might be compatible” with her protein structure. In response, applicant is reminded that a reference is relied upon for the totality of its teachings wherein KOEHL teaches the claimed method, as set forth previously and reiterated above. Further, it is again noted that the instant claims fail to recite the argued limitations; i.e. there is no step of evaluating “other” amino acids recited in the instant claims.

For the reasons previously set forth and set forth above, the rejection is maintained and new claim 67 is rejected.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Applicant merely argues in the response filed 11/26/04 that as KOEHL does not teach the claimed inventions, the combinations of references set forth below do not make obvious the claims. As the examiner maintains that KOEL teaches the claimed methods, the rejections set forth below are also maintained.

Claims 1, 4-8, 12-14, 16, 18-22, 24, 27-29, 41-47, 49, 51-56, 64-65, and 67 are rejected under 35 U.S.C. 103(a) as being unpatentable over KOEHL et al. (J. Molec. Biol. (1994) vol. 239, pp. 249-275) in view of KOEHL et al. (Current Opinion Struct. Bio. (1996) vol. 6, pp. 222-226).

KOEHL (1994) teaches a computerized method of generating a global conformational (probability) matrix representing a protein structure, as set forth above. KOEHL does not teach a Monte Carlo algorithm to generate an ensemble of proteins.

KOEHL (1996) teaches a mean field Monte Carlo procedure to generate a family (ensemble) of proteins, and teaches that this provides significant improvement in an SCMF method of modeling proteins (p. 224).

It would have been obvious to one of ordinary skill in the art at the time of invention to have included the Monte Carlo generation of KOEHL (1996) in the method

of KEOHL (1994) where the motivation would have been to improve the SCMF method of modeling proteins, as taught by KOEHL.

Claims 2-3, 25-26, 38-40, 48, 50, 60-61 and 68 are rejected under 35 U.S.C. 103(a) as being unpatentable over KOEHL et al. (J. Molec. Biol. (1994) vol. 239, pp. 249-275) in view of KOEHL et al. (Current Opinion Struct. Bio. (1996) vol. 6, pp. 222-226) as applied to claims 1, 4-8, 12-14, 16, 18-22, 24, 27-29, 41-47, 49, 51-56, 64-65, and 67 above, and further in view of DAHIYAT et al. (Protein Sci. (1996) vol. 5, pp. 895-903).

KOEHL and KOEHL teach and make obvious a computerized method of generating a global conformational (probability) matrix representing a protein structure, as set forth above. KOEHL (1994) further teaches that her method may be used to predict target structures based on her energy calculations (p. 254).

Neither KOEHL teaches generation or selection of a protein or proteins generated/designed by the method.

DAHIYAT teaches a method of designing proteins from a backbone and rotamer library using a Monte Carlo algorithm (p. 901) and teaches selection and synthesis of the peptide library designed (p. 902). DAHIYAT teaches that proteins may be selected for stability (p. 895:Abstract).

It would have been obvious to one of ordinary skill in the art at the time of invention to have selected and synthesized peptides, as taught by DAHIYAT which were generated in the method of KOEHL and KOEHL, where the motivation would have

been to compare predicted to actual activity and stability of the peptides, as taught by DAHIYAT (abstract and p. 902).

Conclusion

Claims 1-8, 12-14, 16, 18-22, 24-29, 38-56, 60-61, 64-65, and 67-68 are rejected; claims 15, 17, 23, 30-37, 57-59, 62-63 and 66 are withdrawn.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marjorie A. Moran whose telephone number is (571) 272-0720. The examiner can normally be reached on Mon,Wed: 7-1:30; Tue,Thur: 7:30-6; Fri 7-3:30 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on (571)272-0718. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Marjorie A. Moran
Primary Examiner
Art Unit 1631

Marjorie A. Moran
3/21/05